REMARKS

Upon entry of the present amendment, claims 1-27, 29-30, 37-44, and 46 have been cancelled, claims 28 and 45 have been amended and new claims 53 and 54 are presented for examination on the merits. The cancellation of claims 1-27, 29-30, 37-44, and 46 and amendment of claims 28 and 45 are made without prejudice or disclaimer and Applicants reserve the right to prosecute claims directed to the cancelled subject matter and/or the subject matter removed from claims 28 and/or 45 in a continuation or divisional application. Support for the amended claims and the new claims can be found throughout the specification and original claims (e.g., with reference to US Pat. App. Pub. No. 2006/0199762, paragraphs 0108, 0111, 0113-0119, 0122-0124, 0129, 0131-0136, claims 13, 15, 16, and 27). Accordingly, no new matter has been introduced by the new claims or amendments.

Interview Summary

Applicants appreciate the courteous telephonic interview with the Examiner conducted on September 8, 2009 and the helpful comments provided therein. Applicants' representative and the Examiner discussed the pending rejections of record, in particular, amendments to avoid the introduction of new matter and the obviousness rejections. Applicants' representative and the Examiner also discussed the possibility of providing a declaration that shows the unexpected results of the topical formulations. An agreement with the Examiner was not reached.

Claim Objections

The Examiner objected to claims 35, 43, and 51 as being substantial duplicates of claims 30, 38, and 46, respectively. Although Applicants disagree with the conclusion of the Examiner, in an effort to expedite prosecution of the application, Applicants have cancelled claims 30, 38, and 46 without prejudice or disclaimer. Applicants request that the objections to claims 35, 43, and 51 be withdrawn.

Claim Rejections – 35 USC §112

The Examiner has rejected claims 28-52 under 35 USC §112 for introduction of "new matter." The Examiner argues that the specification does not disclose nor define what constitutes "enhanced wound healing," "selecting a mammal having a skin ulcer," and "analyzing the formation of granulation tissue." With respect to claims 45-52, the Examiner argues that the claims do not make clear how the drugs are topically administered if the skin has already been contacted with the wound covering agent. The Examiner also argues that the specification does not disclose the wound covering agents in combination with ointments, creams, and fatty acid esters and the specification does not disclose the manufacturing of wound covering agents or the selection criteria for choosing a particular wound covering agent. The Examiner further argues that the claims are not limited to sealing-type wound covering agents, which provide a wet environment at a wound and allow oxygen and water steam to permeate without permeating liquid and bacteria.

With respect to claim 28 and the dependent claims that rely thereon, Applicants have amended the claims to recite methods for promoting granulation formation and enhanced enclosure of a skin ulcer of a mammal comprising treating a mammal having a skin ulcer with a therapeutically effective amount of a drug comprising a protein of the sequence of SEQ ID NO: 1, wherein said drug is administered to said skin ulcer of said mammal topically. Support for "enhanced enclosure of a skin ulcer" can be found in paragraph 0136, which states that the skin ulcer enclosure rate was enhanced. The "selection" and "analysis" limitations have been removed from the present claim set without prejudice or disclaimer and Applicants reserve the right to prosecute claims that include these limitations in a continuation and/or divisional application.

With respect to claim 45 and the dependent claims that rely thereon, Applicants have amended the claims to recite methods for promoting granulation formation and enhanced enclosure of a skin ulcer of a mammal comprising treating a mammal having a skin ulcer with a therapeutically effective amount of a drug that comprises a protein of the sequence of SEQ ID

NO: 1, wherein said drug is administered to said skin ulcer of said mammal topically; providing a sealing-type wound covering agent selected from the group consisting of a hydrocolloid dressing material, a hydrogen dressing material, a polyurethane dressing material, a hydropolymer dressing material, a hydrofiber dressing material, and a polyurethane foam; and contacting the skin ulcer of said mammal with said wound covering agent. Applicants note that paragraphs 0122, 0123, 0124, and 0129 all describe the use of various types of sealing-type wound covering agents some of which include combination with an external preparation as described in the application. Paragraph 0123 states:

> As a form of combination use of the external preparation of the present invention and a sealing-type wound covering material, the external preparation may be contained in a sealing-type wound covering material or after the external preparation of the present invention may be coated, a damaged site is covered with a sealing-type wound covering material, or after a damaged site is covered with a sealing-type wound covering material, the external preparation of the present invention may be injected with, for example, an injector.

Paragraphs 0113-0119 describe various external preparations including ointments, gels, creams, liquids, and aerosols some of which may also include fatty acid esters and antiseptics (*see e.g., paragraph 0115 and 117).* Accordingly, Applicants assert that the present claims and specification do in fact make clear how the drugs are topically administered if the skin has already been contacted with the wound covering agent, the specification discloses the wound covering agents in combination with ointments, creams, and fatty acid esters and the specification discloses the manufacturing of wound covering agents. Applicants respectfully submit that the new matter rejections raised by the Examiner have been fully addressed and request that the rejections under 35 USC §112 be withdrawn.

Claim Rejections – 35 USC §103

The Examiner has rejected claims 28-52 for being obvious in light of Toyoda et al., in view of Seki et al., Nakamura et al. (US Pat. No. 5,342,831 or EP461,560), Yoshida et al., Morishita et al (US Pat. No. 7,247,620 or WO 02/089854), and DeBusk et al. The Examiner argues that Toyoda et al. discloses that over expression of full-length HGF in transgenic mice

promotes granulation. The Examiner argues that Seki et al. discloses dHGF (corresponding to SEQ. ID. No. 1 of Applicants' specification). The Examiner further argues that Nakamura et al. (EP461,560) discloses that dHGF has the same biological activities as full-length HGF and that Nakamura et al (US Pat. No. 5,342,831) discloses using topical formulations containing full-length HGF to treat skin ulcers. The Examiner additionally argues that Yoshida et al. disclose that the inhibition of full-length HGF using antibodies inhibits granulation tissue formation, that Morishita et al. disclose treating diabetic skin ulcers by topically applying a gene encoding HGF so as to promote granulation, and that DeBusk et al. discloses using hydrocolloid dressings to treat skin ulcers and to promote granulation formation. Based on the combination of the aforementioned references, the Examiner has concluded that it would have been obvious to substitute the dHGF disclosed by Seki et al. and Nakamura et al. (EP461,560) to treat diabetic ulcers as suggested by Morishita et al., Nakamura et al. (US Pat. No. 5,342,831) and Toyoda et al. and to use such formulations in conjunction with the wound covering agents taught by DeBusk et al. The Examiner states that based on the teachings of Seki et al. and Nakamura et al. (EP461,560), one of ordinary skill in the art would have expected that dHGF and HGF both have the ability to promote granulation.

With respect to Applicants prior response, the Examiner argues that although the references provided by the Applicants disclose functional and structural differences between dHGF and full-length HGF, the biological effect is comparable by virtue of the fact that the two molecules both cause signaling through the same receptor. The Examiner also recognizes that the structural and functional differences were known to those of ordinary skill in the art prior to filing the subject application. Nevertheless, the Examiner concludes that this information would have informed one of ordinary skill in the art as to how to modify a dHGF preparation to compensate for the level of heparin binding, degree of solubility, and mitogenic activity level but would not have led them away from using dHGF. The Examiner further argues that it was not unexpected that dHGF and HGF differ in structure or in degree or kind of function and that Applicants have not established that the deletion mutant has an activity change that would lead

one of skill in the art to doubt the known effect of HGF in granulation or enhanced wound healing.

The present claims require that a mammal having a skin ulcer is treated with a therapeutically effective amount of a drug comprising a protein of the sequence of SEQ ID NO: 1, wherein said drug is administered to said skin ulcer of said mammal topically. Respectfully, the Examiner has not fully appreciated the state of the art at the time of filing the present application, the difficulties involved in formulating mutant proteins that have poor solubility into topical preparations and the uncertainties of using a topical preparation to treat skin ulcers. The Examiner asserts that the biological effect of dHGF and full-length HGF is comparable because the two molecules stimulate the same receptor; however, the prior art is replete with examples of similarly structured ligands for the same receptor that produce considerably different patterns of cellular signaling and functional results (e.g., v-src and c-src and the FGF super family). The Examiner asserts that the prior art teaches one how to modify a dHGF preparation to compensate for the level of heparin binding, reduced solubility, and reduced mitogenic activity level but has provided no evidence of such. Although one of skill in the art is certainly able to make minor modifications and adjustments to protein formulations, in this case, modification of protein formulations in a topical drug to compensate for reduced heparin binding, reduced solubility, and reduced mitogenic activity is an unreasonable leap, especially since the claims now require treating the mammal.

The Examiner also asserts that the Applicants have not established that the deletion mutant has an activity change that would lead one of skill in the art to doubt the known effect of HGF in granulation or enhanced wound healing. Applicants again point out that the fact that dHGF has reduced heparin binding, reduced solubility, and reduced mitogenic activity would lead one of skill in the art to think there is no reasonable expectation of success of developing a topical drug that treats skin ulcers. In further support of Applicants arguments that one of skill in the art at the time of filing of the present application would have no reasonable expectation of success, Applicants submit Li et al., which establishes that angiogenesis is critical to wound

repair (Exhibit A, abstract). As demonstrated in Shima et al., dHGF is less potent than full-length HGF in mitogenic activity on human umbilical vein endothelial cells (HUVEC) (*see Fig. 2A*). Accordingly, dHGF also has a reduced potential to promote angiogenesis, a function required for wound repair.

In sum, the prior art at the time of filing the present application recognized that dHGF stimulated the c-met receptor differently than HGF, dHGF has a 70-fold reduced solubility compared to HGF, dHGF has a reduced affinity for heparin compared to HGF, dHGF has a reduced mitogenic activity compared to HGF, and dHGF has a reduced potential for angiogenesis compared to HGF. Additionally, given the difficulties in formulation of HGF into a drug (*see Morishita et al.*) and the uncertainties of achieving a skin ulcer treatment, Applicants submit that one of skill in the art would not have had a reasonable expectation of success at arriving at the claimed invention. Despite these difficulties and uncertainties, the Applicants have developed a topical dHGF formulation that is presently in human clinical trials. In view of the present amendments and arguments above, Applicants respectfully request that the Examiner withdraw the obviousness rejection.

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, Applicant is not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. Applicant reserves the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that Applicant has made any disclaimers or disavowals of any subject matter supported by the present application.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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